

Application No.: 09/733,773

Attorney Docket No.: SALK2410

Filing Date: December 8, 2000

(088802-5651)

Response to Office Action (mailed September 16, 2004) faxed January 18, 2005

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Remarks

In accordance with the present invention, there are provided the crystal structure and atomic coordinates of a Pin1 WW domain co-complexed with a Pin1 WW domain binding agent. The invention provides methods of identifying Pin1 WW domain binding agents employing such crystal structure and atomic coordinates. The invention further provides computer programs for use in developing Pin1 WW domain binding agents.

By the present communication, claims 1, 3, 12 and 18 have been amended to define Applicants' invention with greater particularity. These amendments add no new matter as they are fully supported by the specification and original claims. In addition, claims 2 and 19-28 have been cancelled herein without prejudice. Accordingly, claims 1, 3-12 and 18 remain pending and under active consideration. The present status of all claims in the application is provided in the Listing of Claims presented herein beginning on page 2.

**The Rejection under 35 U.S.C. § 112, First Paragraph—Enablement**

The rejection of claims 1-12 and 18 under 35 U.S.C. § 112, first paragraph, as the specification allegedly fails to enable any person skilled in the art to use the invention commensurate in scope with the claims, is respectfully traversed. Applicants respectfully submit that the claims are fully enabled by the specification.

The standard for determining enablement is whether the specification as filed provides sufficient information so as to permit one skilled in the art to make and use the claimed invention (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* “[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation would proceed” (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Indeed, a thorough evaluation of the “Wands factors” (*In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) confirms that the present claims are fully enabled.

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**a) The quantity of experimentation needed to make and/or use the invention (see page 3 of the Office Action)**

In this section of the Office Action, the Examiner has provided no support for the conclusion that the steps contemplated by the claimed methods constitute undue experimentation. Contrary to the Examiner's assertion, each of the steps contemplated by the claimed methods are well known in the art, and can be readily carried out by one of skill in the art.

**b) The amount of direction and guidance provided by Applicant (see page 3 of the Office Action)**

The specification provides substantial direction and guidance with respect to WW domains contemplated for use in the practice of the present invention. For example, the specification provides exemplary groups of classes of WW domains known in the art, of which the Pin1 WW domain is an exemplary member (see specification at page 5, lines 1-15). Furthermore, the atomic coordinates of the Pin1 WW domain provided in Table 1 of the present application provide a useful way to solve the structure of other crystal forms of WW domains (see specification at page 13, lines 7-13). Accordingly, it is respectfully submitted that the amount of direction or guidance provided by the present specification is commensurate in scope with the claims.

**c) The presence or absence of working examples (see page 4 of the Office Action)**

The present claims are fully supported by working examples included in the specification.

Indeed, as acknowledged by the Examiner, the specification provides working examples of protein purification and crystallography, binding analysis and affinity analysis with exemplary WW domains. What more need be shown? Absolutely no basis has been provided to question the results presented in the Examples, or to question the suggested scope of operability thereof set forth in Applicants' specification.

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**d) The nature of the invention (see page 4 of the Office Action)**

The Examiner has incorrectly characterized the invention, which is drawn to methods for determining the ability of a potential binding agent to compete with a known binding agent for binding to a defined class of agents, i.e., WW domains.

**e) The state of the prior art (see page 4 of the Office Action)**

The Examiner has incorrectly characterized the state of the prior art. The fact that "binding domains vary greatly" (see page 4, line 7 of the Office Action) is an unreasonable over generalization. Contrary to the implication of the above-quoted assertion by the Examiner, the present claims are not directed to any binding domain, but instead are directed specifically to WW domains.

**f) The relative skill of those in the art (see page 4 of the Office Action)**

The Examiner correctly acknowledges that the relevant level of skill in the art is high.

**g) The predictability of the art (see page 4 of the Office Action)**

The Examiner's discussion of WW domains at the bottom of page 4 of the Office Action improperly focuses exclusively on the differences between different WW domains. While there may be differences between such domains, there is far more in common between various WW domains, otherwise they would not all be recognized as belonging to a single class. Thus, when properly considered in the context of the present disclosure, i.e., in view of the findings disclosed herein, the question with respect to predictability of the art is more appropriately phrased in terms of whether it would be predictable to extrapolate from experimentally observed properties of the exemplary Pin1 WW domain, as demonstrated herein, to other members of the same class, i.e., WW domains. It is respectfully submitted that such extrapolation would be expected, with a high likelihood, to accurately predict the properties of other members of the same class of agents, i.e., WW domains.

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**h) The breadth of the claims (see page 5 of the Office Action)**

The Examiner's assertion that "[t]he claims are broad because they are drawn to determining any known WW domain binding agent" once again mischaracterizes the invention. Contrary to the Examiner's assertion, the claims are directed to methods of identification of specific agents, which methods require specific manipulations (contacting, modeling, crystal formation, etc) with specific components to obtain the desired result. Accordingly, it is respectfully submitted that the specification provides more than adequate enablement of all of the components contemplated for use in the invention methods.

Moreover, in efforts to reduce the issues and expedite prosecution, claims 1 and 18 have been amended herein to define the claimed subject matter with even greater particularity. For example, claim 1 has been amended to make consistent reference to Pin1 WW domains, consistent with the Examiner's acknowledgment that the claims are enabled for Pin1 WW domains (see page 2, line 17 of the Office Action).

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-12 and 18 under 35 U.S.C. § 112, first paragraph.

**The Rejection under 35 U.S.C. § 103(a)**

The rejection of claims 1-6, 8, 9, 11, 12 and 18 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Ranganathan *et al.* (*Cell* 89:875-886, 1997), in view of Lu *et al.* (U.S. Patent No. 6,495,376), in further view of Klebe (*J. Mol. Med* 78:269-281, 2000), is respectfully traversed. Applicants respectfully submit that none of these references, either taken alone or in combination, teaches or suggests the methods of the present invention.

Thus, invention methods, as defined, for example, by claim 1, distinguish over Ranganathan *et al.* by requiring contacting the potential binding agent with a Pin1 WW domain in the presence of a Pin1 WW domain substrate. Moreover, Applicants' invention further distinguishes over Ranganathan *et al.* by specifically using a plurality of atomic coordinates obtained from a Pin1 WW domain crystallized in co-complex with a known Pin1 WW domain binding agent, substrate, or inhibitor to model a potential binding agent.

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In contrast, Ranganathan *et al.* study the structure of Pin1 to determine its functional properties (*i.e.*, the catalytic mechanism of its peptidyl-prolyl cis-trans isomerase activity). Indeed, as acknowledged by the Examiner, "Ranganathan *et al.* do not disclose contacting binding agents and determining the ability of the agent to bind" (see page 7, lines 6-7 of the Office Action).

Lu *et al.* is unable to overcome the deficiencies of the primary reference, because Lu *et al.* does not teach or suggest the claimed methods. The present invention, as defined by claim 1, distinguishes over Lu *et al.* by requiring the computer modeling of a potential binding agent based on atomic coordinates obtained from crystals of a Pin1 WW domain. Applicants' method relies on binding agents whose three-dimensional structures indicate they are likely to have robust interactions with a Pin1 WW domain. In contrast, Lu *et al.* merely discloses the interaction of WW domain-containing polypeptides with ligands using only traditional binding assays (for example, incubating an uncharacterized test compound with a WW domain polypeptide).

Moreover, Lu *et al.* does not disclose either contacting a potential binding agent identified by modeling of atomic coordinates with a Pin1 WW domain, or the determination or use of atomic coordinates obtained from a Pin1 WW domain crystallized in co-complex with a known Pin1 WW domain binding agent, substrate, or inhibitor.

Further reliance on Klebe is unable to cure the deficiencies of the combination of Ranganathan and Lu. Contrary to the Examiner's assertion, no motivation exists, absent Applicant's disclosure, to combine the 3 references now relied upon in efforts to render obvious the present claims. Such use of Applicants' disclosure is clearly improper.

Indeed, there is no motivation to use the functional studies provided in Ranganathan *et al.* to model potential WW domain binding agents. In efforts to provide motivation for the methods of the present invention, at page 8 of the Office Action, the Examiner quotes Ranganathan *et al.*, which states "[s]tructural studies of Pin1 complexes with native substrates and systematic mutagenesis of Pin1 residues implicated in catalysis and substrate recognition should help

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resolve the mechanism of Pin1-dependent cell cycle regulation" (emphasis added, Ranganathan *et al.*, at page 884). Clearly, the use of native substrates in mechanistic studies cannot suggest the computer modeling of unknown potential binding agents to identify WW domain binding agents.

Similarly, there is no motivation to use the methodology described in Klebe to model potential WW domain binding agents. In further efforts to provide motivation for the methods of the present invention, at page 9 of the Office Action, the Examiner asserts that "motivation is provided by Klebe, who clearly indicates that structure-based design is a universal tool for understanding the principals of protein-ligand complexes and drug design." Where is the motivation to apply this "universal tool" to the specific circumstances contemplated by the present claims? It is only with improper benefit of Applicants' disclosure that the applied combination of references can be asserted.

Indeed, the only motivation for further reliance on Klebe is found in the Examiner's acknowledgment, without refutation, of Applicants' prior assertion that "Lu *et al.* is unable to overcome the deficiencies of Ranganathan *et al.* because Lu *et al.* do not teach computer modeling." (See page 10, lines 7-8 of the Office Action). Instead of clarifying the basis on which the combination of Ranganathan *et al.* and Lu *et al.* allegedly renders the present claims obvious, the Examiner reaches for another incremental teaching (i.e., Klebe). The resulting rejection, based on a combination of three references, can be seen to be nothing more than a house of cards, one unrelated disclosure coupled with another unrelated disclosure.

Therefore, none of the cited references (Ranganathan *et al.*, Lu *et al.* and Klebe), either taken alone or in combination, teaches or suggests the claimed methods. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-6, 8, 9 and 11-18 under 35 U.S.C. § 103(a).

### Conclusion

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved in view of

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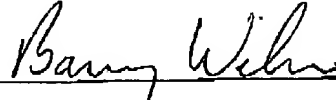
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this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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